Remarks Regarding New Claims:

Support for new Claim 19 is found on page 2 of the specification. Amendments to Claims 1, 2, 5 and 6 relate to only the removal of a single species from a Markush description for the element U. This amendment is not meant as a limitation in any way on any of the other elements of these claims.

RESPONSE

112 Lack of Enablement

The Office Action rejected Claims 9-18 as lacking enablement for disorders other than rheumatoid arthritis.

Applicants request clarification as to the nature of this rejection. MPEP 2164.07 states, "To avoid confusion during examination, any rejection under 35 U.S.C. 112, first paragraph, based on grounds other than lack of utility should be imposed separately from any rejection imposed due to 'lack of utility' under 35 U.S.C. 101 and 35 U.S.C. 112, first paragraph. The Office Action states that "[f]or a compound or a genus to be effective against inflammation generally is contrary to medical science." The language of the rejection dictates that this rejection is of the type addressed by MPEP 2164.07. Accordingly, Applicants respectfully submit that this section also addresses the burdens of the parties in sustaining and rebutting the rejection.

When an Office Action states that a utility is contrary to medical principles, the burden starts on the Office to provide evidence showing that one of ordinary skill in the art would reasonably doubt the asserted utility. Once the Office has met this burden, the burden shifts to the Applicants to provide rebuttal evidence sufficient to convince one of ordinary skill in the art of the invention's asserted utility. The Applicants' evidence does not need to establish utility beyond a reasonable doubt, but merely be enough to lead a person of ordinary skill in the art to conclude that the asserted utility is more likely than not true. Once the Applicants have provided evidence, it is essential for the Office personnel to recognize, fully consider and respond to each substantive element of any response to a rejection based on lack of utility. MPEP 2107.02.VI.

The Office Action rejected the Claims as contrary to medical science, but provided external evidence that one skilled in the art would find the asserted utility unbelievable.

Applicants respectfully point to MPEP 2107.03, which addresses the special care needed to sustain a utility rejection based on an asserted therapeutic use.

If the Office wishes to establish a *prima facie* case of lack of enablement, the Office Action must show that the specification does not enable one of skill in the art to make and use the invention without undue experimentation. *See In re Wands*, 8 U.S.P.Q.2d at 1404 (Fed. Cir. 1988). While the Office Action lists the factors to be considered under Wands, it fails to analyze all of the factors in light of the facts of the present application.

Quantity of Experimentation Necessary

The Office Action does not address this element. Applicants respectfully point out that the specification teaches how to make the claimed compounds, how to test them for efficacy, which indication they could be useful for, and how to administer them to a patient in need thereof. The Office Action does not comment on the amount of experimentation or what type of experimentation would be needed over and above that provided in the specification.

Amount of Direction or Guidance Presented

The specification in this case supplies information on how to make the claimed compounds (pp. 72-147), multiple assays with which to select the most active compounds (pp. 153-159), which indications the compounds may be used to treat (pp. 1-8), the dosage information for the compounds (pp. 43, 46), and instruction as to the formulations to be administered (pp. 40-46). The specification details how to make the treatment from compound to formulation and provides a list of indications in order to show how the formulations and doses should be used.

Presence or Absence of Working Examples

The specification in this case contains more than 120 diverse examples of compounds as well as examples of formulation types. Accordingly, the number of examples is sufficient to support the existing claims.

Nature of the Invention

The Office Action states that the functions of the vitronectin molecule are poorly understood and it is difficult to establish the overall regulatory role of vitronectin. But the only support for this argument comes from 1992 and 1994 publications. The Applicants specification documents recent publications that provide a more current picture of the state of the art. However, the Office Action fails to address any of these publications. The publications are as follows:

bone resorption (Endocrinology 137:2347-54, 1996; J. Endocrinol. 154(Suppl.):S47-S56, 1997),

cell attachment, spreading and migration (Int. J. Biochem. Cell Biol. 31:539-544, 1999; Carreitas et al., Int. J. Cancer 80:285-294, 1999),

signal transduction, cell to cell interactions and is upregulated in response to vascular damage (Int. J. Biochem. Cell Biol. 29:721-725, 1997)

tumor cell invasion, angiogenesis, wound healing, phagocytosis of apototic cells and inflammation (J. Cell Biol. 144:767-775, 1999; Drug News Perspect. 10:456-461, 1997; Am. J. Pathol. 148:1407-1421, 1996)

tumor growth and hypercalcemia of malignancy (Cancer Res. 58:1930-1935, 1998)

tumorigenicity of human melanoma cells (Natali et al., Cancer Res. 57:1554-60, 1997)

melanoma metastasis (Cancer Metastasis Rev. 14:241-245, 1995; Cancer Metastasis Rev. 10:3-10, 1991)

viral infections (J. Virol. 72:3587-3594, 1998; Virology 203:357-65, 1994)

endocytosis and degradation of vitronectin (J. Biol. Chem. 268:11492-5, 1993)

cellular locomotion of human keratinocytes (J. Biol. Chem. 269:26926-32, 1994)

tumor cell metastasis (J. Clin. Invest. 99:1390-1398, 1997)

differentiation of neuroblastoma metastasis (Am. J. Pathol. 150:1631-1646, 1997)

viral infections (Nat. Med. (N.Y.) 5:78-82, 1999; J. Cell Biol. 127:257-64, 1994).

carcinoma cell proliferation (J. Biol. Chem. 127:547-56, 1994)

wound healing and cell attachment (J. Invest. Dermatol. 106:42-8, 1996)

epithelial inflammation, such as asthma (J. Cell Biol. 133:921-928, 1996)

tumor cell spreading and proliferation in colon cancer cells (Biochem. Biophys. Res. Commun. 249:287-291, 1998; Int. J. Cancer 81:90-97, 1999)

regulation of pulmonary inflammation and fibrosis and binding and activating transforming growth factor β1 (Munger et al., Cell (Cambridge, Mass) 96:319-328, 1999)

viral infections (Virology 239:71-77, 1997)

State of the Prior Art

See above.

Relative Skill of Those in the Art

The relative skill in the art is similar to the standard found in other pharmaceutical application.

Predictability in the Art

The Office Action states, "Receptor activity is generally an unpredictable and highly structure specific area." However, the Office provides no support for such statement. The above references show that compounds that activate the subject receptors to be therapeutics for the indications listed. The Applicants have provided the means by which to make and evaluate drug candidates within the scope of the claims.

Scope of the Claims

The main focus of the rejection is found in the statement, "There is no reasonable basis for assuming that the myriad of compounds embraced by the instant claims will all share the same physiological properties since they are so structurally dissimilar as to be chemically nonequivalent and there is no basis in the prior art for assuming the same." Applicants respectfully disagree with this statement. The structural similarity is shown by claimed structure which represents a restriction grouping suggested in the Office Action dated 28 January 2002. The specification shows that the compounds of the invention, supported by over 120 diverse examples, have activity at the subject receptor. The Office Action contains no rebuttal evidence as to why the claims should be considered to advance too far beyond the exemplified compounds.

However, in order to advance prosecution in this case, Applicants have amended the claims.

The Applicants believe that--in light of an analysis of all of the *Wands* factors--the Office Action fails to establish why, or what kind of, undue experimentation would be required. Accordingly, Applicants request reconsideration of the rejection.

The Applicants thank the Examiner for the comments on the enablement of rheumatoid arthritis and have accordingly added new Claim 19.

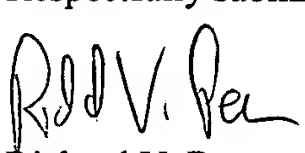
103Rejections

The Office Action rejected Claims 1-2 and 4-18 as being unpatentable over Abood et al. While the Applicants do not agree with the Office's evaluation, in an effort to advance prosecution the Applicants have amended the claims to remove amidino from the definition of U, to further distinguish the present invention from the cited reference.

Conclusion

Applicants respectfully submit that Claims 1-2 and 4-19 as amended are patentable over the prior art of record, and urge allowance of these claims and passage to issue of the present application. Moreover, Applicants' attorney sincerely and respectfully requests that the Examiner consider, a telephone (805-447-3299) or personal interview to resolve any outstanding issues deemed appropriate by the Examiner.

Respectfully submitted,



Richard V. Person
Attorney for Applicants
Registration No.: 42,991
Phone: (805) 447-3299
Date: June 20, 2002

Please send all future correspondence to:

US Patent Operations/RVP
Dept. 4300, M/S 27-4-A
AMGEN INC.
One Amgen Center Drive
Thousand Oaks, California 91320-1799

Marked-up changes:

1. (Twice Amended) A compound of the formula

$$U\text{-}V\text{-}A\text{-}(Alk)_j\text{-}(C(O)\text{-}NH)_h\text{-}(Alk)_g\text{-}B$$

or a pharmaceutically acceptable salt thereof, wherein g, h and j are each independently 0 or 1; provided when h is 0, then g is 0;

each Alk is independently a alkyl radical;

U represents ~~amidino,~~ guanidino, -(G-alkyl)$_k$-NH-R_1, -(G-alkyl)$_k$-NH-C(Q)-R_1, -(G-alkyl)$_k$-C(Q)-N(R)-R_1, -(G-alkyl)$_k$-NH-C(Q)-N(R)-R_1, -(G-alkyl)$_k$-NH-C(Q)-O-R_1 or -(G-alkyl)$_k$-O-C(Q)-N(R)-R_1 radical; or U represents a hydroxyalkyl-G- radical which is optionally substituted by a cycloalkyl, aryl, heteroaryl or heterocyclyl, wherein the cycloalkyl, aryl, heteroaryl and heterocyclyl radicals are optionally substituted by 1-3 radicals of R_2;

wherein k is 0 or 1;

G represents a bond, O, S or NH;

Q represents O, S, NH, N-CN or N-alkyl;

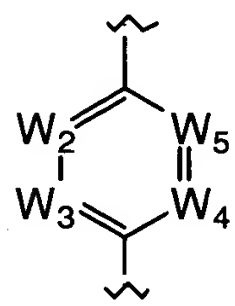
R is a radical of hydrogen or alkyl;

R_1 is a radical of alkyl, haloalkyl, $R_{21}R_{22}$N-alkyl, R_{21}O-alkyl, R_{21}S-alkyl, cycloalkyl, cycloalkyl-alkyl, aryl, aryl-alkyl, heteroaryl, heteroaryl-alkyl, heterocyclyl or heterocyclyl-alkyl, wherein the cycloalkyl, aryl, heteroaryl and heterocyclyl radicals are optionally substituted by 1-3 radicals of R_2;

wherein R_{21} and R_{22} are each independently a radical of hydrogen, alkyl, haloalkyl, cycloalkyl, cycloalkyl-alkyl, aryl, aryl-alkyl, heteroaryl, heteroaryl-alkyl, heterocyclyl or heterocyclyl-alkyl, wherein the cycloalkyl, aryl, heteroaryl and heterocyclyl radicals are optionally substituted by 1-3 radicals of R_2;

each R_2 is independently a halo, alkyl, alkoxy, alkylthio, haloalkyl, haloalkoxy, hydroxy, carboxy, cyano, azido, amidino, guanidino, nitro, amino, alkylamino or dialkylamino radical or two adjacent R_2 radicals on an aryl or heteroaryl radical represent a methylenedioxy, ethylenedioxy or propylenedioxy radical;

V represents a radical of formula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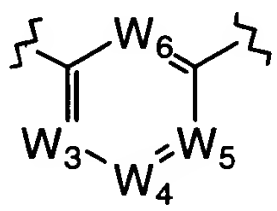
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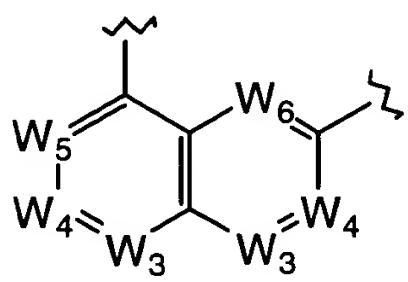
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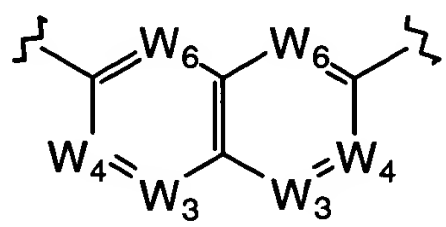
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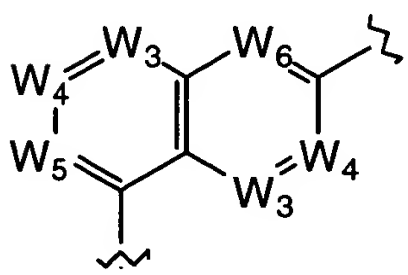
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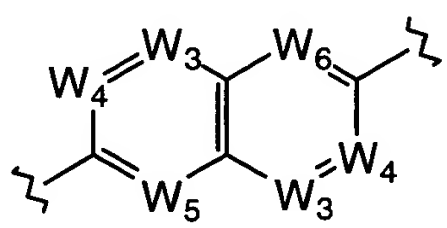
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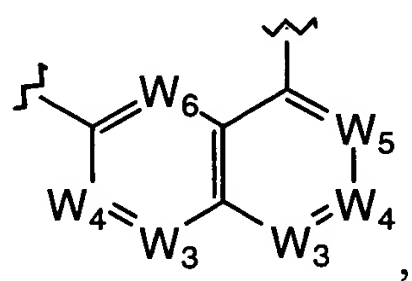
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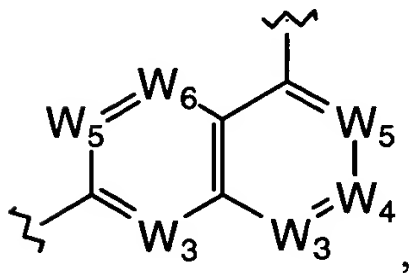
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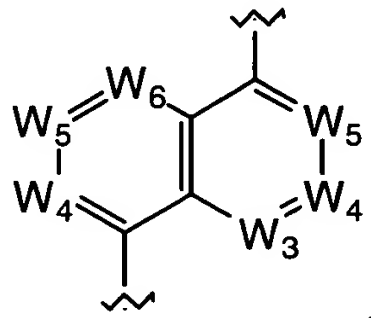

,

wherein each W_2, W_3, W_4 and W_5 is C-R_4; provided the total number of cycloalkyl, aryl, heteroaryl, heterocyclyl, carboxy, -C(O)-O-R_{19}, -C(O)-R_{19}, -C(O)-NH-R_{19}, -C(O)-N(R_{19})$_2$ and -R_{19} radicals in W_2, W_3, W_4 and W_5 is 0-2;

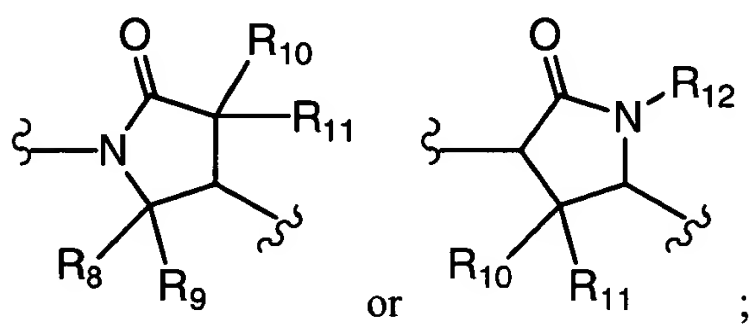
each W_6 is C-H; and

each R_4 is independently a hydrogen, halo, alkyl, alkoxy, alkylthio, haloalkyl, haloalkoxy, hydroxy, cyano, carboxy, -C(O)-O-R_{19}, -C(O)-R_{19}, -C(O)-NH-R_{19}, -C(O)-N(R_{19})$_2$, cycloalkyl, cycloalkyl-alkyl, aryl, aryl-alkyl, heteroaryl, heteroaryl-alkyl, heterocyclyl or heterocyclyl-alkyl radical, wherein the cycloalkyl, aryl, heteroaryl and heterocyclyl radicals are optionally

substituted by 1-3 radicals of R_2; or two adjacent R_4 radicals taken together with the carbon atoms to which they are attached represent a fused-phenyl or fused-heteroaryl of 5-6 ring members, wherein the phenyl and heteroaryl radicals are optionally substituted by 1-3 radicals of R_2;

R_5, R_6 and R_7 are each independently a hydrogen, halo, alkyl, alkoxy, alkylthio, haloalkyl, haloalkoxy, hydroxy or cyano radical; or R_5 and R_6 or R_6 and R_7 taken together with the carbon atoms to which they are attached represent a fused-phenyl or fused-heteroaryl of 6 ring members, wherein the phenyl and heteroaryl radicals are optionally substituted by 1-3 radicals of R_2; or R_3 and R_6 taken together with the carbon atoms to which they are attached represent a fused-heteroaryl of 6 ring members optionally substituted by 1-3 radicals of R_2;

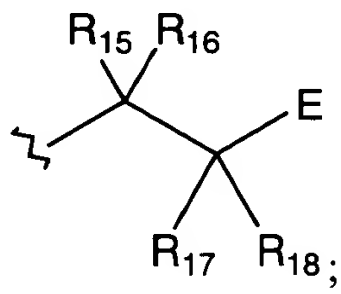
A represents a radical of formula



;

R_8, R_9, R_{10}, R_{11} and R_{12} are each independently a hydrogen or alkyl radical; or $-CR_8R_9-$ represents a -C(O)-;

B represents a radical of formula



;

wherein (a) R_{15} is a hydrogen or alkyl radical; and R_{17} is (1) an aryl, heteroaryl, -NH-C(O)-R_{19}, -C(O)-NH-R_{19}, -NH-C(O)-NH-R_{19}, -O-C(O)-NH-R_{19}, -NH-C(O)-O-R_{19}, -$S(O)_2$-R_{19}, -NH-$S(O)_2$-R_{19}, -$S(O)_2$-NH-R_{19} or -NH-$S(O)_2$-NH-R_{19} radical, or (2) an alkyl radical substituted by a radical of aryl, heteroaryl, -NH-C(O)-R_{19}, -C(O)-NH-R_{19}, -NH-C(O)-NH-R_{19}, -O-C(O)-NH-R_{19}, -NH-

$C(O)$-O-R_{19}, -$S(O)_2$-R_{19}, -NH-$S(O)_2$-R_{19}, -$S(O)_2$-NH-R_{19} or -NH-$S(O)_2$-NH-R_{19}; wherein the aryl and heteroaryl radicals are optionally substituted by 1-3 radicals of R_2; or

(b) R_{17} is a hydrogen or alkyl radical; and R_{15} is (1) an aryl, heteroaryl, cycloalkyl, heterocyclyl, -NH-$C(O)$-R_{19}, -$C(O)$-NH-R_{19}, -NH-$C(O)$-NH-R_{19}, -O-$C(O)$-NH-R_{19}, -NH-$C(O)$-O-R_{19}, -$S(O)_2$-R_{19}, -NH-$S(O)_2$-R_{19}, -$S(O)_2$-NH-R_{19} or -NH-$S(O)_2$-NH-R_{19} radical, or (2) an alkyl radical substituted by a radical of aryl, heteroaryl, cycloalkyl, heterocyclyl, -NH-$C(O)$-R_{19}, -$C(O)$-NH-R_{19}, -NH-$C(O)$-NH-R_{19}, -O-$C(O)$-NH-R_{19}, -NH-$C(O)$-O-R_{19}, -$S(O)_2$-R_{19}, -NH-$S(O)_2$-R_{19}, -$S(O)_2$-NH-R_{19} or -NH-$S(O)_2$-NH-R_{19} radical; wherein the cycloalkyl, aryl, heteroaryl and heterocyclyl radicals are optionally substituted by 1-3 radicals of R_2;

provided that when a nitrogen atom is attached to the carbon atom to which R_{15} is attached, then R_{15} is (1) an aryl, heteroaryl, cycloalkyl, heterocyclyl or -$C(O)$-NH-R_{19} radical, or (2) an alkyl radical substituted by a radical of aryl, heteroaryl, cycloalkyl, heterocyclyl, -NH-$C(O)$-R_{19}, -$C(O)$-NH-R_{19}, -NH-$C(O)$-NH-R_{19}, -O-$C(O)$-NH-R_{19}, -NH-$C(O)$-O-R_{19}, -$S(O)_2$-R_{19}, -NH-$S(O)_2$-R_{19}, -$S(O)_2$-NH-R_{19} or -NH-$S(O)_2$-NH-R_{19};

wherein R_{19} is a alkyl, cycloalkyl, cycloalkyl-alkyl, aryl, aryl-alkyl, heteroaryl, heteroaryl-alkyl, heterocyclyl or heterocyclyl-alkyl, wherein the cycloalkyl, aryl, heteroaryl and heterocyclyl radicals are optionally substituted by 1-3 radicals of R_2;

R_{16} and R_{18} are each independently a hydrogen or alkyl radical; and

E is a radical of carboxy, amido, tetrazolyl, -$C(O)$-O-R_{20}, -$C(O)$-NH-R_{20}, -$C(O)$-NH-$S(O)$-R_{20}, -$C(O)$-NH-$S(O)_2$-R_{20} or -$C(O)$-NH-$C(O)$-R_{20};

wherein R_{20} is an alkyl, cycloalkyl, aryl, heteroaryl or heterocyclyl radical or an alkyl radical substituted by 1-3 radicals of halo, hydroxy, carboxy, amino, cycloalkyl, aryl, heteroaryl or heterocyclyl, wherein the cycloalkyl, aryl, heteroaryl and heterocyclyl radicals are optionally substituted by 1-3 radicals of R_2; and

provided that when U represents amidino, guanidino, -C(Q)-NH-R_1 or -NH-C(Q)-NH-R_1 radical, wherein Q represents NH, N-CN or N-alkyl, then at least one of g, h or j is 1.

2. (Amended) The compound of Claim 1 or a pharmaceutically acceptable salt thereof, wherein

each Alk is independently a C_1-C_{12} alkyl radical;

U represents ~~**amidino,**~~ guanidino, -(G-(C_1-C_8 alkyl))$_k$-NH-R_1, -(G-(C_1-C_8 alkyl))$_k$-NH-C(Q)-R_1, -(G-(C_1-C_8 alkyl))$_k$-C(Q)-N(R)-R_1, -(G-(C_1-C_8 alkyl))$_k$-NH-C(Q)-N(R)-R_1, -(G-(C_1-C_8 alkyl))$_k$-NH-C(Q)-O-R_1 or -(G-(C_1-C_8 alkyl))$_k$-O-C(Q)-N(R)-R_1 radical; or U represents a hydroxy(C_1-C_{12} alkyl)-G- radical which is optionally substituted by a C_3-C_8 cycloalkyl, aryl, heteroaryl of 5-10 ring members or heterocyclyl of 5-8 ring members, wherein the cycloalkyl, aryl, heteroaryl and heterocyclyl radicals are optionally substituted by 1-3 radicals of R_2;

Q represents O, S, NH, N-CN or N-(C_1-C_8 alkyl);

R is a radical of hydrogen or C_1-C_8 alkyl;

R_1 is a radical of C_1-C_8 alkyl, halo(C_1-C_8 alkyl) of 1-7 halo radicals, $R_{21}R_{22}$N-(C_1-C_8 alkyl), R_{21}O-(C_1-C_8 alkyl), R_{21}S-(C_1-C_8 alkyl), C_3-C_8 cycloalkyl, C_3-C_8 cycloalkyl(C_1-C_8 alkyl), aryl, aryl(C_1-C_8 alkyl), heteroaryl of 5-10 ring members, heteroaryl(C_1-C_8 alkyl) of 5-10 ring members, heterocyclyl of 5-8 ring members or heterocyclyl(C_1-C_8 alkyl) of 5-8 ring members, wherein the cycloalkyl, aryl, heteroaryl and heterocyclyl radicals are optionally substituted by 1-3 radicals of R_2;

wherein R_{21} and R_{22} are each independently a radical of hydrogen, C_1-C_8 alkyl, halo(C_1-C_8 alkyl) of 1-7 halo radicals, C_3-C_8 cycloalkyl, C_3-C_8 cycloalkyl(C_1-C_8 alkyl), aryl, aryl(C_1-C_8 alkyl), heteroaryl of 5-10 ring members, heteroaryl(C_1-C_8 alkyl) of 5-10 ring members, heterocyclyl of 5-8 ring members or heterocyclyl(C_1-C_8 alkyl) of 5-8 ring members, wherein the cycloalkyl, aryl, heteroaryl and heterocyclyl radicals are optionally substituted by 1-3 radicals of R_2;

each R_2 is independently a halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 alkylthio, halo(C_1-C_4 alkyl) of 1-5 halo radicals, halo(C_1-C_4 alkoxy) of 1-5 halo radicals, hydroxy, carboxy, cyano, azido, amidino, guanidino, nitro, amino, C_1-C_8 alkylamino or di(C_1-C_8 alkyl)amino radical or two adjacent R_2 radicals on an aryl or heteroaryl radical represent a methylenedioxy, ethylenedioxy or propylenedioxy radical;

each R_3 is independently a hydrogen or C_1-C_6 alkyl radical;

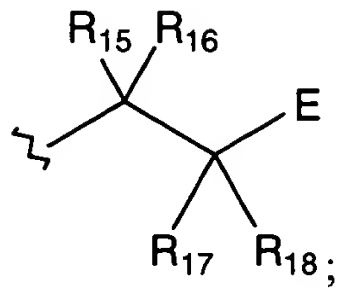
each R_4 is independently a hydrogen, halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 alkylthio, halo(C_1-C_4 alkyl) of 1-5 halo radicals, halo(C_1-C_4 alkoxy) of 1-5 halo radicals, hydroxy, cyano, carboxy, -C(O)-O-R_{19}, -C(O)-R_{19}, -C(O)-NH-R_{19}, -C(O)-N(R_{19})$_2$, C_3-C_6 cycloalkyl, C_3-C_6 cycloalkyl(C_1-C_4 alkyl), aryl, aryl(C_1-C_4 alkyl), heteroaryl of 5-10 ring members, heteroaryl(C_1-C_4 alkyl) of 5-10 ring members, heterocyclyl of 5-8 ring members or heterocyclyl(C_1-C_4 alkyl) of 5-8 ring members radical, wherein the cycloalkyl, aryl, heteroaryl and heterocyclyl radicals are optionally substituted by 1-3 radicals of R_2; or two adjacent R_4 radicals taken together with the carbon atoms to which they are attached represent a fused-phenyl or fused-heteroaryl of 5-6 ring members, wherein the phenyl and heteroaryl radicals are optionally substituted by 1-3 radicals of R_2;

R_5, R_6 and R_7 are each independently a hydrogen, halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 alkylthio, halo(C_1-C_4 alkyl) of 1-5 halo radicals, halo(C_1-C_4 alkoxy) of 1-5 halo radicals, hydroxy or cyano radical; or R_5 and R_6 or R_6 and R_7 taken together with the carbon atoms to which they are attached represent a fused-phenyl or fused-heteroaryl of 6 ring members, wherein the phenyl and heteroaryl radicals are optionally substituted by 1-3 radicals of R_2; or R_3 and R_6 taken together with the carbon atoms to which they are attached represent a fused-heteroaryl of 6 ring members optionally substituted by 1-3 radicals of R_2;

X_2 is C-H, C-(C_1-C_4 alkyl), a C_3-C_8 spirocycloalkyl or spiroheterocyclyl of 5-8 ring members radical; wherein the spirocycloalkyl and spiroheterocyclyl radicals are optionally substituted by an oxo or thiooxo radical and 1-2 radicals of C_1-C_6 alkyl, halo(C_1-C_4 alkyl) of 1-5 halo radicals, hydroxy, C_1-C_6 alkoxy or halo(C_1-C_4 alkoxy) of 1-5 halo radicals;

R_8, R_9, R_{10}, R_{11} and R_{12} are each independently a hydrogen or C_1-C_6 alkyl radical; or -CR_8R_9- represents a -C(O)-;

B represents a radical of formula



wherein (a) R_{15} is a hydrogen or C_1-C_6 alkyl radical; and R_{17} is (1) an aryl, heteroaryl of 5-10 ring members, -NH-C(O)-R_{19}, -C(O)-NH-R_{19}, -NH-C(O)-NH-R_{19}, -O-C(O)-NH-R_{19}, -NH-C(O)-O-R_{19}, -$S(O)_2$-R_{19}, -NH-$S(O)_2$-R_{19}, -$S(O)_2$-NH-R_{19} or -NH-$S(O)_2$-NH-R_{19} radical, or (2) an C_1-C_6 alkyl radical substituted by a radical of aryl, heteroaryl of 5-10 ring members, -NH-C(O)-R_{19}, -C(O)-NH-R_{19}, -NH-C(O)-NH-R_{19}, -O-C(O)-NH-R_{19}, -NH-C(O)-O-R_{19}, -$S(O)_2$-R_{19}, -NH-$S(O)_2$-R_{19}, -$S(O)_2$-NH-R_{19} or -NH-$S(O)_2$-NH-R_{19}; wherein the aryl and heteroaryl radicals are optionally substituted by 1-3 radicals of R_2; or

(b) R_{17} is a hydrogen or C_1-C_6 alkyl radical; and R_{15} is (1) an aryl, heteroaryl of 5-10 ring members, C_3-C_8 cycloalkyl, heterocyclyl of 5-8 ring members, -NH-C(O)-R_{19}, -C(O)-NH-R_{19}, -NH-C(O)-NH-R_{19}, -O-C(O)-NH-R_{19}, -NH-C(O)-O-R_{19}, -$S(O)_2$-R_{19}, -NH-$S(O)_2$-R_{19}, -$S(O)_2$-NH-R_{19} or -NH-$S(O)_2$-NH-R_{19} radical, or (2) an C_1-C_4 alkyl radical substituted by a radical of aryl, heteroaryl of 5-10 ring members, C_3-C_8 cycloalkyl, heterocyclyl of 5-8 ring members, -NH-C(O)-R_{19}, -C(O)-NH-R_{19}, -NH-C(O)-NH-R_{19}, -O-C(O)-NH-R_{19}, -NH-C(O)-O-R_{19}, -$S(O)_2$-R_{19}, -NH-$S(O)_2$-R_{19}, -$S(O)_2$-NH-R_{19} or -NH-$S(O)_2$-NH-R_{19} radical; wherein the cycloalkyl, aryl, heteroaryl and heterocyclyl radicals are optionally substituted by 1-3 radicals of R_2;

provided that when a nitrogen atom is attached to the carbon atom to which R_{15} is attached, then R_{15} is (1) an aryl, heteroaryl, cycloalkyl, heterocyclyl or -C(O)-NH-R_{19} radical, or (2) an alkyl radical substituted by a radical of aryl, heteroaryl, cycloalkyl, heterocyclyl, -NH-C(O)-R_{19}, -C(O)-NH-R_{19}, -NH-C(O)-NH-R_{19}, -O-C(O)-NH-R_{19}, -NH-C(O)-O-R_{19}, -$S(O)_2$-R_{19}, -NH-$S(O)_2$-R_{19}, -$S(O)_2$-NH-R_{19} or -NH-$S(O)_2$-NH-R_{19};

wherein R_{19} is a C_1-C_6 alkyl, C_3-C_8 cycloalkyl, C_3-C_8 cycloalkyl(C_1-C_6 alkyl), aryl, aryl(C_1-C_6 alkyl), heteroaryl of 5-10 ring members, heteroaryl(C_1-C_6 alkyl) of 5-10 ring members, heterocyclyl of 5-8 ring members or heterocyclyl(C_1-C_6 alkyl) of 5-8 ring members, wherein the cycloalkyl, aryl, heteroaryl and heterocyclyl radicals are optionally substituted by 1-3 radicals of R_2;

R_{16} and R_{18} are each independently a hydrogen or C_1-C_6 alkyl radical; and

R_{20} is a C_1-C_6 alkyl, C_3-C_8 cycloalkyl, aryl, heteroaryl of 5-10 ring members or heterocyclyl of 5-8 ring members radical or a C_1-C_6 alkyl radical substituted by 1-3 radicals of halo, hydroxy, carboxy, amino, C_3-C_8 cycloalkyl, aryl, heteroaryl of 5-10 ring members or heterocyclyl of 5-8 ring members, wherein the cycloalkyl, aryl, heteroaryl and heterocyclyl radicals are optionally substituted by 1-3 radicals of R_2.

5. (Twice Amended) The compound of Claim 4 or a pharmaceutically acceptable salt thereof, wherein

each Alk is independently a C_1-C_4 alkyl radical;

U represents ~~amidino,~~ guanidino, -(G-(C_1-C_8 alkyl))$_k$-NH-R_1, -(G-(C_1-C_8 alkyl))$_k$-NH-C(Q)-R_1, -(G-(C_1-C_8 alkyl))$_k$-C(Q)-N(R)-R_1, -(G-(C_1-C_8 alkyl))$_k$-NH-C(Q)-N(R)-R_1 or -(G-(C_1-C_8 alkyl))$_k$-NH-C(Q)-O-R_1 radical;

G represents a bond, O or NH;

Q represents O, S, NH, N-CN or N-(C_1-C_4 alkyl);

R is a radical of hydrogen or C_1-C_4 alkyl;

R_1 is a radical of C_1-C_6 alkyl, halo(C_1-C_6 alkyl) of 1-5 halo radicals, $R_{21}R_{22}$N-(C_1-C_6 alkyl), R_{21}O-(C_1-C_6 alkyl), C_3-C_8 cycloalkyl, C_3-C_8 cycloalkyl(C_1-C_6 alkyl), aryl, aryl(C_1-C_6 alkyl), heteroaryl of 5-10 ring members, heteroaryl(C_1-C_6 alkyl) of 5-10 ring members, heterocyclyl of

5-8 ring members or heterocyclyl(C_1-C_6 alkyl) of 5-8 ring members, wherein the cycloalkyl, aryl, heteroaryl and heterocyclyl radicals are optionally substituted by 1-3 radicals of R_2;

R_{21} and R_{22} are each independently a radical of hydrogen, C_1-C_8 alkyl, aryl, aryl(C_1-C_4 alkyl), heteroaryl of 5-10 ring members or heteroaryl(C_1-C_4 alkyl) of 5-10 ring members, wherein the aryl and heteroaryl radicals are optionally substituted by 1-3 radicals of R_2;

each R_2 is independently a halo, C_1-C_4 alkyl, C_1-C_4 alkoxy, C_1-C_4 alkylthio, halo(C_1-C_2 alkyl) of 1-5 halo radicals, halo(C_1-C_2 alkoxy) of 1-5 halo radicals, hydroxy, carboxy, cyano, azido, amidino, guanidino, nitro, amino, C_1-C_4 alkylamino or di(C_1-C_4 alkyl)amino radical or two adjacent R_2 radicals on an aryl or heteroaryl radical represent a methylenedioxy, ethylenedioxy or propylenedioxy radical;

each R_4 is independently a hydrogen, halo, C_1-C_4 alkyl, C_1-C_4 alkoxy, C_1-C_4 alkylthio, halo(C_1-C_2 alkyl) of 1-5 halo radicals, halo(C_1-C_2 alkoxy) of 1-5 halo radicals, hydroxy, cyano, carboxy, -C(O)-O-R_{19}, -C(O)-R_{19}, -C(O)-NH-R_{19}, -C(O)-N(R_{19})$_2$, C_3-C_6 cycloalkyl, C_3-C_6 cycloalkyl(C_1-C_4 alkyl), aryl, aryl(C_1-C_4 alkyl), heteroaryl of 5-10 ring members, heteroaryl(C_1-C_4 alkyl) of 5-10 ring members, heterocyclyl of 5-8 ring members or heterocyclyl(C_1-C_4 alkyl) of 5-8 ring members radical, wherein the cycloalkyl, aryl, heteroaryl and heterocyclyl radicals are optionally substituted by 1-3 radicals of R_2; and

R_{20} is a C_1-C_4 alkyl, aryl or heteroaryl of 5-10 ring members or a C_1-C_4 alkyl radical substituted by 1-3 radicals of halo, hydroxy, carboxy, amino, aryl, heteroaryl of 5-10 ring members or heterocyclyl of 5-8 ring members, wherein the aryl, heteroaryl and heterocyclyl radicals are optionally substituted by 1-3 radicals of R_2.

6. (Amended) The compound of Claim 5 or a pharmaceutically acceptable salt thereof, wherein

U represents ~~**amidino,**~~ guanidino, -(G-(C_1-C_8 alkyl))$_k$-NH-R_1, -NH-C(Q)-R_1, -(G-(C_1-C_8 alkyl))$_k$-C(Q)-N(R)-R_1, -NH-C(Q)-N(R)-R_1 or -NH-C(Q)-O-R_1 radical;

Q represents O or NH;

R is a radical of hydrogen or C_1-C_2 alkyl;

R_1 is a radical of C_1-C_6 alkyl, halo(C_1-C_6 alkyl) of 1-5 halo radicals, $R_{21}R_{22}N$-(C_1-C_4 alkyl), $R_{21}O$-(C_1-C_4 alkyl), C_3-C_8 cycloalkyl, C_3-C_8 cycloalkyl(C_1-C_4 alkyl), aryl, aryl(C_1-C_4 alkyl), heteroaryl of 5-10 ring members, heteroaryl(C_1-C_4 alkyl) of 5-10 ring members, heterocyclyl of 5-8 ring members or heterocyclyl(C_1-C_4 alkyl) of 5-8 ring members, wherein the cycloalkyl, aryl, heteroaryl and heterocyclyl radicals are optionally substituted by 1-3 radicals of R_2;

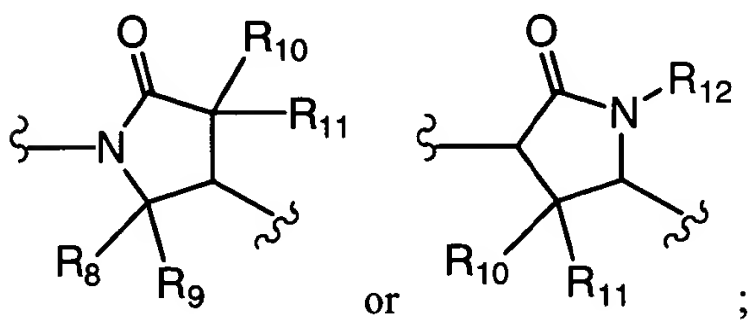
R_{21} and R_{22} are each independently a radical of hydrogen, C_1-C_6 alkyl, aryl or heteroaryl of 5-10 ring members, wherein the aryl and heteroaryl radicals are optionally substituted by 1-3 radicals of R_2;

each R_2 is independently a halo, C_1-C_2 alkyl, C_1-C_2 alkoxy, C_1-C_2 alkylthio, CF_3-, CF_3O-, hydroxy, carboxy, cyano, azido, amidino, guanidino, nitro, amino, C_1-C_2 alkylamino or di(C_1-C_2 alkyl)amino radical or two adjacent R_2 radicals on an aryl or heteroaryl radical represent a methylenedioxy, ethylenedioxy or propylenedioxy radical;

each W_2, W_3, W_4 and W_5 are independently C-R_4;

each R_4 is independently a hydrogen, halo, C_1-C_4 alkyl, C_1-C_4 alkoxy, C_1-C_4 alkylthio, halo(C_1-C_2 alkyl) of 1-5 halo radicals, halo(C_1-C_2 alkoxy) of 1-5 halo radicals, hydroxy or cyano radical;

A represents a radical of formula



;

(a) R_{15} is a hydrogen or C_1-C_2 alkyl radical; and R_{17} is -NH-C(O)-R_{19}, -NH-C(O)-NH-R_{19}, -NH-C(O)-O-R_{19}, -NH-$S(O)_2$-R_{19} or -NH-$S(O)_2$-NH-R_{19} radical; or (b) R_{17} is a hydrogen or C_1-C_2 alkyl radical; and R_{15} is (1) an aryl, heteroaryl of 5-10 ring members, C_3-C_8 cycloalkyl or heterocyclyl of 5-8 ring members radical, or (2) an C_1-C_2 alkyl radical substituted by a radical of aryl, heteroaryl of 5-10 ring members, C_3-C_8 cycloalkyl or heterocyclyl of 5-8 ring members radical; wherein the cycloalkyl, aryl, heteroaryl and heterocyclyl radicals are optionally substituted by 1-3 radicals of R_2;

R_{19} is a C_1-C_4 alkyl, aryl, aryl(C_1-C_4 alkyl), heteroaryl of 5-10 ring members or heteroaryl(C_1-C_4 alkyl) of 5-10 ring members, wherein the aryl and heteroaryl radicals are optionally substituted by 1-3 radicals of R_2;

R_{16} and R_{18} are each independently a hydrogen or C_1-C_4 alkyl radical;

E is a radical of carboxy, amido, tetrazolyl or -C(O)-O-R_{20}; and

R_{20} is a C_1-C_2 alkyl, aryl or heteroaryl of 5-10 ring members or a C_1-C_2 alkyl radical substituted by 1-3 radicals of halo, hydroxy, carboxy, aryl or heteroaryl of 5-10 ring members, wherein the aryl and heteroaryl radicals are optionally substituted by 1-3 radicals of R_2.